OVARIAN CARCINOMA: PATHOLOGY, STAGING, GRADING, AND PROGNOSIS*

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OVARIAN cancer is a serious problem in the management of neoplastic disease. To focus a review of the pathology, clinical staging, histologic grading, and prognosis the 133 cases accessioned in the Lenox Hill Hospital Tumor Registry, 1967-1971, representing 3.3% of the total cancers registered, are listed in Table I.

These cases were classified by at least six different pathologists and, after review of the slides of the undifferentiated carcinomas, many probably could be placed in other categories. For the past three years at Lenox Hill Hospital ovarian cancers have been studied by a team that included Dr. Margaret Long, cytologist and histochemist; Dr. Harry L. Ioachim, who utilized tissue culture and immunopathology; and Miss Barbro Andersson, electron-microscopy technician.

In all other published series, serous cystadenocarcinoma also is the most common type of ovarian cancer. In earlier reports which did not distinguish endometrioid carcinoma separately, the incidence of serous cystadenocarcinoma ranged from 60 to 75% of all cases. In more recent series which give endometrioid carcinoma group status with other histogenetic types of ovarian tumors, serous neoplasms ranged around 40% in frequency. In the material of Long and Taylor,[1] among the primary ovarian tumors related to Mullerian epithelium, serous cystadenocarcinoma was the commonest cancer, 40%; endometrioid was the second

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TABLE I. THE 133 CASES ACCESSIONED IN THE LENOX HILL HOSPITAL TUMOR REGISTRY, 1967-1971

Serous cystadenocarcinoma	46 cases
Undifferentiated carcinoma	42
Mucinous cystadenocarcinoma	17
Endometrioid carcinoma	6
Metastatic carcinoma	6
Granulosa cell carcinoma	4
Mesonephric carcinoma	3
Dysgerminoma, malignant teratoma, and leiomyosarcoma	1 each
No pathologic examination	6

most common carcinoma, 15.7%; mucinous cystadenocarcinoma, third, 10.8%; and undifferentiated carcinoma, fourth, 6.7%. Kottmeier has reported similar frequencies.[2]

Over-all five-year survivals have been poor in ovarian carcinoma, from 20.6 to 27.7% in seven series compiled during the years 1922 through 1961, comprising more than 6,000 cases.[3] A more recent report by Munnell[4] recorded a five-year survival rate of 40%. Since ovarian carcinoma is not an entity but occurs as several different types of tumors, the grouping of tumors of dissimilar histology and biological activity doubtless has resulted in the differences in survival records. Histologically homogeneous groups of tumors should be analyzed in all clinics for more accurate comparisons of end results. To attain this goal the use of a uniform histologic classification, shown in Table II, has been developed by the Federation Internationale de Gynecologie et Obstetrique (F.I.G.O.)[5] The major primary epithelial tumors are serous cystomas, mucinous cystomas, and unclassified carcinomas. The first three types are subclassified as benign, borderline (those of low potential malignancy), and carcinoma.

Clinical staging of the extent of primary ovarian carcinoma at operation is also essential in developing valid statistics concerning survival so that therapeutic results may be compared more precisely. The F.I.G.O. stages[5] suggested for international use, given in Table III, are quite similar to stages previously used by Kottmeier. Data are now presented that compare the prognosis in Stage Ia, with growth limited to one ovary, and in Stage Ib, with involvement of both ovaries.

The striking differences in prognosis of different clinical stages of ovarian carcinoma are shown in Figure 1, from the Ontario material of

TABLE II. HISTOLOGICAL CLASSIFICATION OF THE COMMON PRIMARY EPITHELIAL TUMORS OF THE OVARY

(Accepted in September 1964)

I. Serous cystomas
   a) Serous benign cystadenoma
   b) Serous cystadenomas with proliferating activity of the epithelial cells and nuclear abnormalities but with no infiltrative destructive growth (low potential malignancy)
   c) Serous cystadenocarcinomas

II. Mucinous cystomas
   a) Mucinous benign cystadenomas
   b) Mucinous cystadenomas with proliferating activity of the epithelial cells and nuclear abnormalities but with no infiltrative destructive growth (low potential malignancy)
   c) Mucinous cystadenocarcinomas

III. Endometrioid tumors (similar to adenocarcinomas in the endometrium)
   a) Endometrioid benign cysts
   b) Endometroid tumors with proliferating activity of the epithelial cells and nuclear abnormalities but with no infiltrative destructive growth (low potential malignancy)
   c) Endometrioid adenocarcinomas

IV. Mesonephroid tumors (clear cell tumors)
   a) Mesonephroid benign cysts
   b) Mesonephroid tumors of low potential malignancy
   c) Mesonephroid adenocarcinomas

V. Concomitant carcinoma, unclassified carcinoma (tumors which cannot be allotted to one of the groups I, II, III, or IV)

MacKay and Sellers,[6] which correlates their results with those of Kottmeier.[7] If Kottmeier's Stages I and II were grouped as "early" and his stages III and IV as "late" cases, there was an equally notable difference in 10-year survivals. Several other series have demonstrated comparable survival differences. Conversely, if various histologic types are grouped rather than separated, the prognostic differences are obscured. Consequently, to clarify briefly the characteristics of groups of ovarian tumors, the common types of ovarian carcinoma will now be considered individually, beginning with the most frequent.

Serous cystadenocarcinoma. Grossly these carcinomas are typically unilocular cysts of various sizes, containing thin yellow fluid, lined partly or completely by small or large granular pale yellow or white protruding papillations resembling raw cauliflower. The cyst wall may be grossly or microscopically invaded by similar granular tissue, and

TABLE III. STAGE GROUPING FOR PRIMARY CARCINOMA OF THE OVARY BASED ON FINDINGS AT CLINICAL EXAMINATION AND SURGICAL EXPLORATION

(Accepted in September 1964)

Stage I. Growth limited to the ovaries
- Stage Ia—Growth limited to one ovary, no ascites
- Stage Ib—Growth limited to both ovaries, no ascites
- Stage Ic—Growth limited to one or both ovaries, ascites present with malignant cells in the fluid

Stage II. Growth involving one or both ovaries with pelvic extension
- Stage IIa—Extension and/or metastasis to the uterus and/or tubes only
- Stage IIb—Extension to other pelvic tissues

Stage III. Growth involving one or both ovaries with widespread intraperitoneal metastasis to the abdomen (the omentum, the small intestine, and its mesentery)

Stage IV. Growth involving one or both ovaries with distant metastasis outside the peritoneal cavity

Special category. Unexplored cases which are thought to be ovarian carcinoma (no explorative or therapeutic surgical treatment having been performed)

Note: The presence of ascites will not influence staging for stages II, II, and IV.

penetrative carcinoma may appear as granular excrescences on the outside of the cyst.

Histologically serous tumors are graded as benign, borderline, and Grades I to III carcinoma. The orderly benign serous cystadenoma cells are columnar, ciliated, and closely resemble fallopian tubal epithelium. "Borderline" changes include slight cytologic irregularities and localized piling up of epithelium on the surfaces of the papillae with mitotic activity. In serous cystadenocarcinoma, Grade I, this piling up of epithelium is accentuated into one or several layers, and some free epithelial cells float in the fluid (Figure 2). Cilia are manifestly present in benign, borderline, and Grade I serous tumors. Grade II serous cystadenocarcinoma is more invasive with some solid areas, but retains differentiated regions with multiple layers of recognizable serous-type cells. Serous cystadenocarcinoma, Grade III, is more undifferentiated; it presents a solid growth pattern but with recognizable papillary type growths (Figure 3). Nuclear and nucleolar anaplastic size variations are more striking in Grade II and particularly in Grade III serous cystadenocarcinomas. Stromal calcospherites, the so-called psammoma bodies, have been considered a hallmark of papillary serous cystadenocarci-

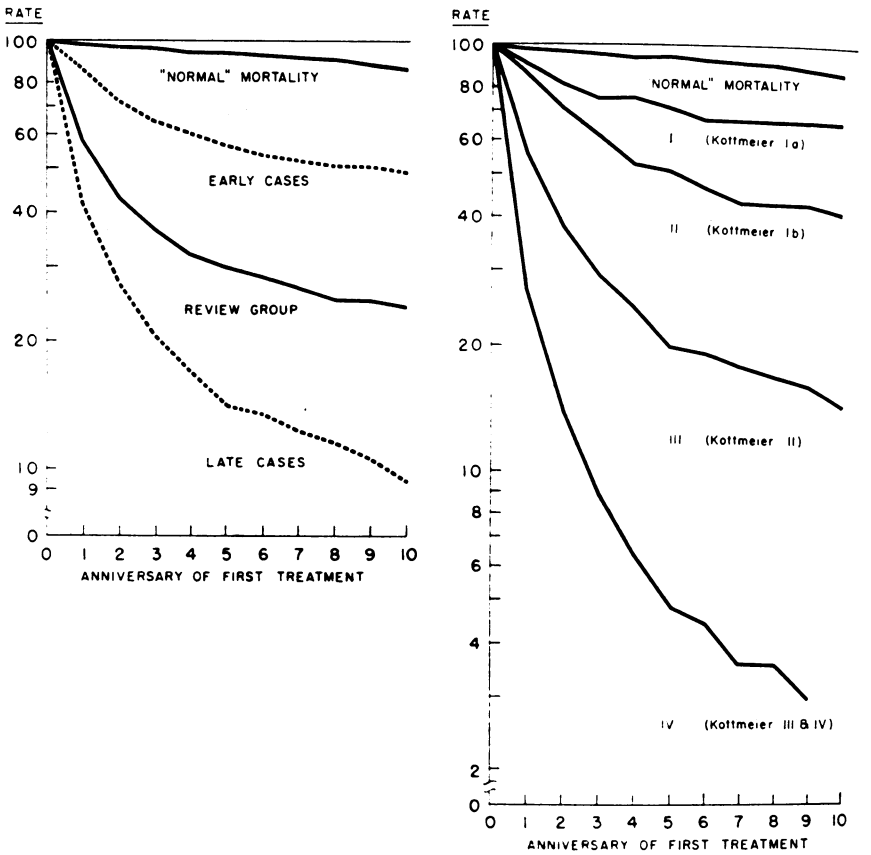

Fig. 1. Crude survival rates at 10-year anniversary by extent and stage. Reproduced by permission from MacKay, E. N. and Sellers, A. H.: *Canad. Med. Ass. J. 96*:299, 1967.

nomas. They may occur, however, in both mucinous and endometrioid tumors.

Significant differences in five-year survivals between the different grades of papillary serous cystadenocarcinoma are shown in Figure 4. While borderline serous tumors have an excellent prognosis, occasional cases die of widespread dissemination, sometimes 15 years after the original diagnosis.

Histochemical grading, after staining the tumor nucleoli specifically for RNA with methyl green pyronin Y, is an extension of histologic grading. Compared to "borderline" serous tumors (Figure 5) in serous cystadenocarcinoma Grade III (Figure 6), overall the nucleoli are twice as large. This implies, in Grade III tumors, more nucleolar RNA. Since

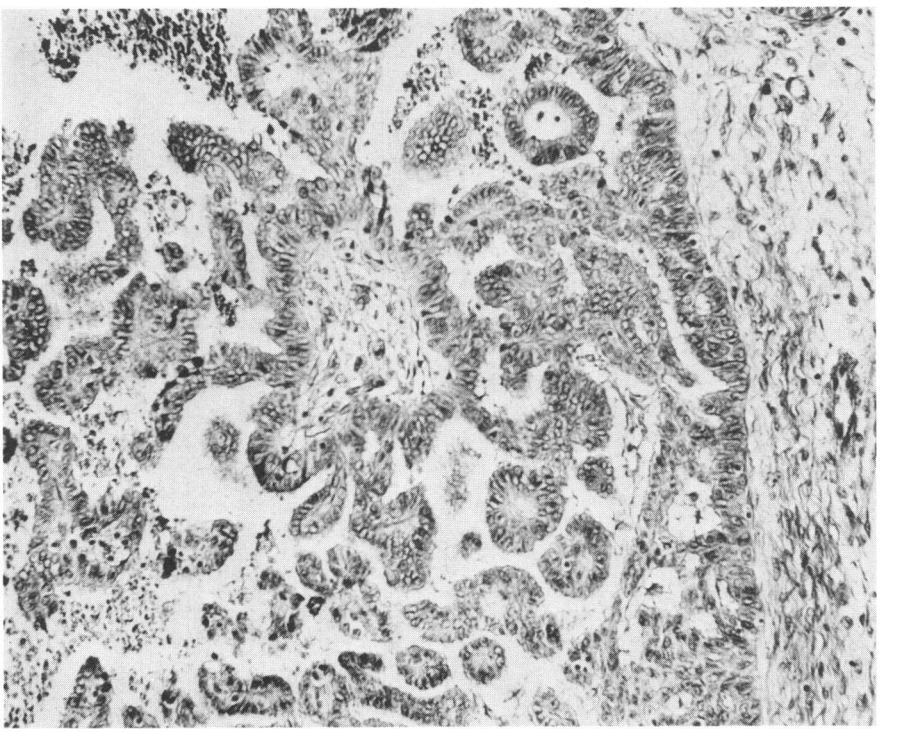

Fig. 2. Papillary serous cystadenocarcinoma, Grade I. Epithelium predominantly of several layers. H & E, × 170.

RNA is associated with protein synthesis and growth of cells, the larger nucleoli, because of their RNA content, correlate with faster growth and higher lethality of Grade III tumors.[8]

Tissue cultures of ovarian serous cystadenocarcinoma show the cells to grow in a characteristic garland pattern. By electron microscopy the carcinoma cells characteristically have extremely convoluted nuclear membranes and large nucleoli. Cytoplasmic secretory granules are present, and the cell surfaces possess irregular microvilli and sometimes cilia. Growing in ascitic fluid or tissue culture, serous cystadenocarcinoma cells become rounded and ultrastructurally maintain the alterations observed in the original tumor.

Undifferentiated carcinoma. Sometimes called solid carcinoma, this tumor may have begun as a specific type but, when discovered, indications of the original cell type are obscured. Microscopically there is a solid proliferation of epithelial cells without identifiable characteristics.

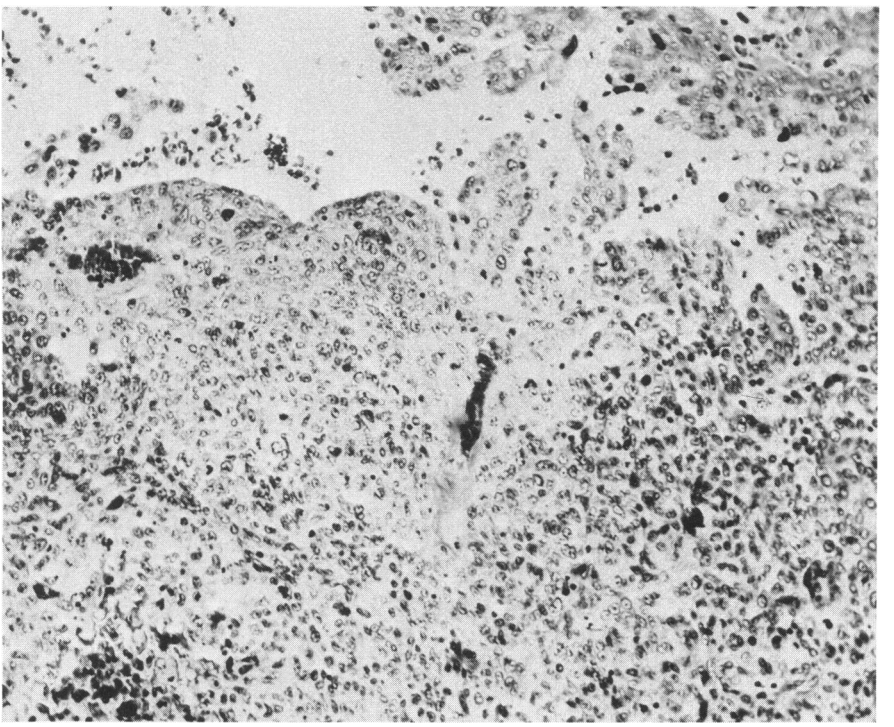

Fig. 3. Papillary serous cystadenocarcinoma, Grade III. Epithelial growth in sheets of cells with papillary indications and cellular anaplasia. H & E, × 170.

Likewise, in tissue culture undifferentiated carcinoma grows in a non-specific pavement pattern. By electron microscopy the nuclei are not as convoluted as in serous cystadenocarcinoma, but there are no specific ultrastructural features permitting classification. The prognosis is generally worse than for other primary ovarian carcinomas.

Mucinous cystadenocarcinoma. Grossly these are multiloculated tumors containing sticky mucin, with solid areas of carcinoma. Microscopically, benign mucinous tumors have a regular, columnar, goblet-cell type of epithelium. In borderline mucinous tumors the epithelium topographically resembles that in serous borderline neoplasms. Mucinous cystadenocarcinomas Grades I to III show progressively more atypism, fewer goblet cells, and a more loculated growth from serous cystomas. Even Grade III mucinous cystadenocarcinomas contain some mucinous goblet cells, but they may be recognized only with special mucicarmine or alcian blue-PAS stains. In tissue culture, the cells characteristically

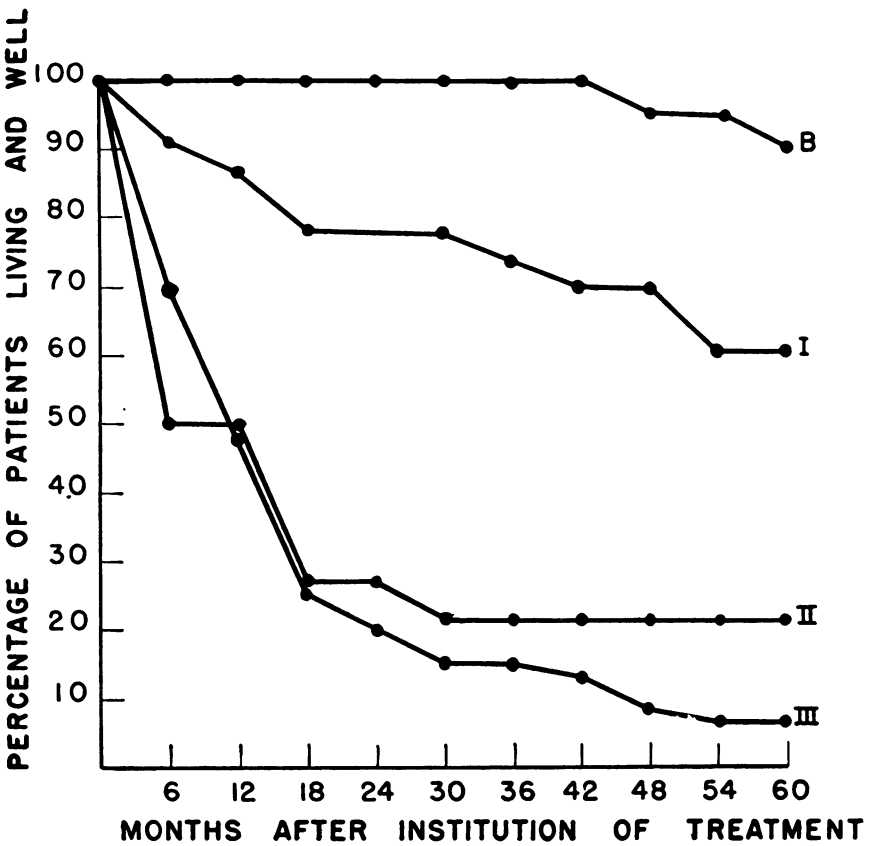

Fig. 4. Five-year survival curves in papillary serous cystadenocarcinoma of ovary according to histologic degree of malignancy (1922-1943). Reproduced by permission from Munnell, E. W. and Taylor, H. C., Jr.: *Amer. J. Obstet. Gynec. 58*:943, 1949.

continue to produce mucin and to form gobletlike cells. By electron microscopy cytoplasmic mucin droplets are identified, and the nuclei are not as polymorphous as in serous cystadenocarcinomas.

At least two reported series indicate that for the same clinical stage there is no significant difference in the prognosis of mucinous and serous cystadenocarcinomas.

Endometrioid carcinoma. Grossly these are solid tan or yellow tumors peripherally, with central areas of degeneration and hemorrhage. This is a relatively recently recognized type of ovarian carcinoma described by Long and Taylor,[1] important because of the relatively favorable prognosis. In their series the absolute five-year survival rate

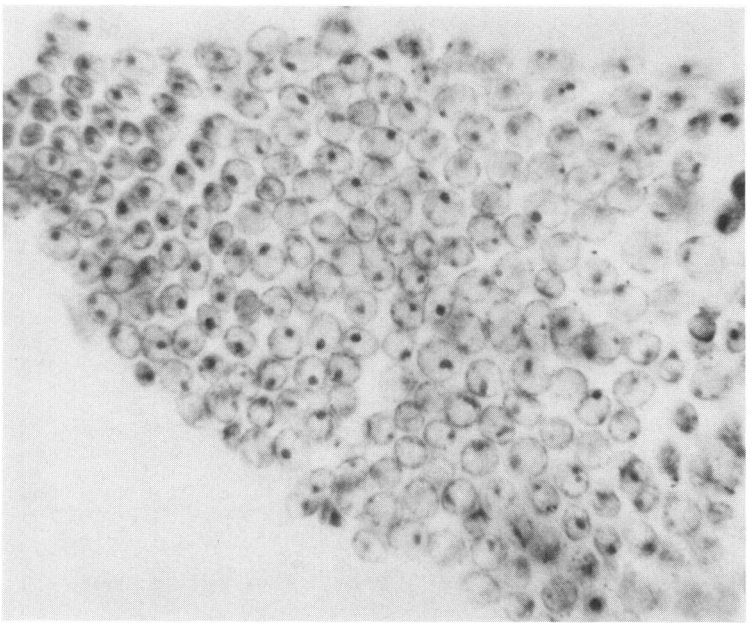

Fig. 5. Papillary serous cystadenocarcinoma, "borderline." Tissue smear showing whole nuclei with single and multiple nucleoli. Single nucleolar mean, 1.5 microns. Methyl green—Pyronin Y, × 918.

was 70%, compared to 33.3% for serous cystadenocarcinoma and 42.7% for the entire series of 89 cases.

Adenocarcinoma arising in ovarian endometriosis is a different entity, represented by a malignant tumor in part of the wall of an ovarian endometriotic cyst. Histologically, in both instances the tumor is indistinguishable from primary endometrial adenocarcinoma. A problem of tumor origin not easily solved arises when the same type of adenocarcinoma is present both in ovary and uterus. It was thought best to exclude such cases from an analysis of a large series of endometrioid carcinomas.

Microscopically, borderline and Grades I to III endometrioid carcinomas are classified by criteria similar to those already described. Foci of squamous metaplasia are common and relatively characteristic of all grades of endometrioid carcinoma of the ovary. Probably most primary adenoacanthomas of the ovary are endometrioid carcinomas. Ultrastructurally their cells grow with a flat surface, and there are microvilli and cilia found on the free-cell margin, besides terminal bars and desmo-

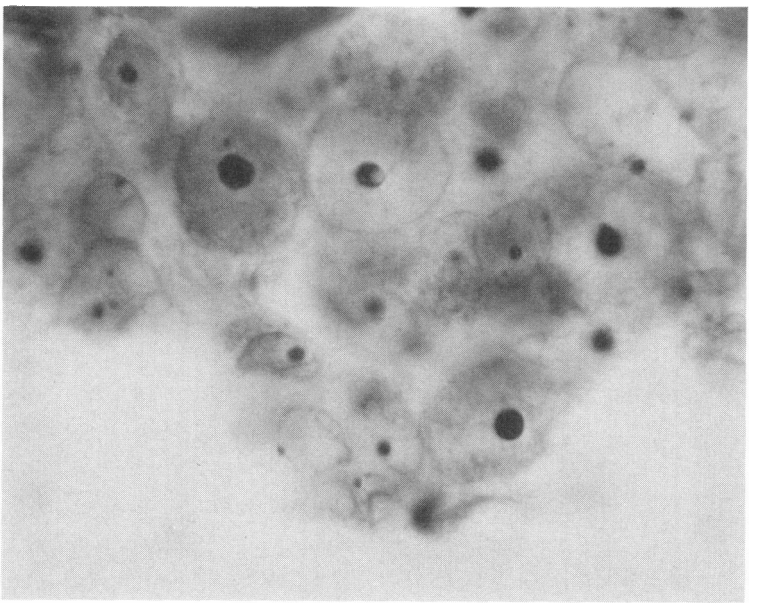

Fig. 6. Papillary serous cystadenocarcinoma, Grade III. Tissue smear as in Figure 4. Single nucleolar mean, 3.0 microns. Methyl green—Pyronin Y, × 918.

somes between adjacent cells. Secretory vacuoles and curious elongated mitochondria are found in the cytoplasm.

Illustrations of histological grading of all the common types of ovarian carcinoma have recently been published by Long and Sommers[9] and so will not be reproduced in this paper.

Metastatic carcinoma. Typically, bilateral, hard, lumpy, solid ovarian tumors are present. Microscopically there may be so much stromal proliferation that the minute foci of carcinoma cells can be overlooked, resulting in a mistaken diagnosis of ovarian fibroma. Krukenberg tumors are the best known metastatic type, the result of spread from a small, inapparent mucinous carcinoma of the stomach or a mucinous carcinoma from one of at least six other sites in the gastrointestinal tract, urinary bladder, and elsewhere. The hallmark of Krukenberg tumor is the signet-ring cell containing mucus in a large cytoplasmic vacuole. Special mucin stains are helpful in difficult cases.

Aside from Krukenberg tumors, metastases to the ovary are commonly from colonic adenocarcinomas, breast carcinomas, lymphomas,

etc. In Burkitt's tumor, an African lymphoma, the ovaries of the youthful patients commonly become greatly enlarged.

Granulosa-cell carcinoma. These most common of the functioning ovarian cancers have a nonspecific, partly cystic and partly solid, tan appearance. The Ovarian Tumor Registry has reported a favorable 77% five-year survival. They are often slowly growing, with recurrences after 20 or even 35 years.

Histologically, there are the well-differentiated folliculoma pattern of Grade I and the less differentiated types, including sarcomatoid growth of Grade III granulosa-cell carcinoma.

Mesonephroma. Grossly these tumors are partly solid, partly cystic, and contain watery or mucoid fluid. Microscopically, the clear-cell type of Schiller, termed mesonephroma or mesometanephroma, are recognizably distinctive, resembling renal-cell carcinomas. We believe mesonephromas to be of urogenital ridge type, like hypernephromas, rather than a Mullerian tumor. It may be seen, however, in Table II that F.I.G.O. includes this type with epithelial ovarian tumors terming them mesonephroid.

Norris and Rabinowitz[10] have recently noted a relatively favorable actuarial survival of 47% at five years and 42% at 10 years in 39 cases, a better result than for serous cystadenocarcinoma. This is not true of the possibly related, very malignant endodermal-sinus tumor of Teilum and yolk-sac-type carcinoma of the ovary.

Dysgerminoma. This solid, pale, soft ovarian tumor is more common in adolescents and young adults, who may have dysgenetic gonads or indications of incomplete development of the female genital system and secondary sex characteristics. Microscopically the tumor consists of cords of clear cells, with intermingled lymphocytes, plasma cells and, sometimes, granulomas with giant cells. Their histologic appearance is identical to that of testicular seminoma or embryonal carcinoma in males.

The prognosis of dysgerminoma is relatively favorable in several series with over 80% five-year survivors.

Several other uncommon types of ovarian cancer exist, including malignant solid teratoma, carcinoma arising in cystic teratoma (dermoid cyst), malignant struma ovarii, primary ovarian carcinoid, stromal sarcomas, etc. For brevity this review has emphasized the most common types of ovarian carcinoma, which are responsible for the bulk of its morbidity and mortality.

SUMMARY

The gross and microscopic pathology, clinical staging, histologic and cytologic grading, tissue-culture growth, electron microscopy, and prognosis of the most common ovarian carcinomas have been reviewed. Clinical staging and histologic grading are essential to understand the course of ovarian cancer. Serous and mucinous cystadenocarcinomas, as well as undifferentiated carcinomas, have the poorest prognosis. Endometrioid carcinoma, granulosa-cell carcinoma, mesonephroma, and dysgerminoma are more favorable types. The control of ovarian cancer is an unsolved problem at present.

Our hope is that the acceptance and use, by all clinics, of the standardized F.I.G.O. clinical stage-grouping and histologic classification of the common epithelial tumors of the ovary will allow therapeutic results throughout the world to be more accurately compared. In addition, careful histologic grading of ovarian carcinomas should further validate end results and, in the future, help improve survival in ovarian carcinoma, which has remained consistently poor over several decades.

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